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| 09/866,067 | 05/23/2001 | Thomas J. Meade | A-58762-20/RFT/RMS/RMK | 7813 |

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EXAMINER

ZITOMER, STEPHANIE W

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|--------------------------------------|-------------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/866,067 | MEADE ET AL. |
| | Examiner Stephanie Zitomer | Art Unit 1634 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 21 August 2002.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 21-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 21-32 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

| | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application status

1. Receipt of the amendment filed August 21, 2002 and the Terminal Disclaimer filed February 26, 2003 is acknowledged.
2. Rejections not reiterated herein from the previous Office action, mailed August 14, 2001, have been withdrawn on reconsideration. Applicant's remarks, now considered moot, have been fully reviewed.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection under 35 U.S.C. 112, first paragraph: New matter

3. Claims 21-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It has been noted that claims 21-32, submitted in the Preliminary Amendment filed July 9, 2001, are drawn to new matter because the subject modified nucleotide triphosphate comprising a covalently attached ETM and method of making a nucleic acid using same are not supported by an explanatory written description as required by the first paragraph of section 112. See the following paragraph 4.

Rejection under 35 U.S.C. 112, first paragraph: Lack of written description

4. Claims 21-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Although Figures 4A and 4B illustrate a nucleoside comprising an electron transfer group in order to demonstrate the attachment to an amino modification on the ribose, the specification fails to describe the claimed "modified nucleotide comprising a covalently attached electron transfer moiety" or the claimed modified nucleotide wherein the electron transfer moiety (ETM) is attached via linker as a molecule that is distinct from a nucleic acid molecule. In the method of making

nucleic acids comprising electron transfer moieties described in the specification at page 20 and in Example 1 at pages 36-42, the nucleotides are modified by addition of an amino group at the 2' or 3' position and the liganded electron transfer moiety is attached via the amino group after synthesis of the nucleic acid in which the amino-modified nucleosides are incorporated (page 20, lines 15-24). Thus, the specification further fails to teach how to make the claimed invention nucleotide with attached electron transfer moiety.

Furthermore, one of skill in the art would not have expected that a nucleotide with attached electron transfer moiety which comprises a liganded transition metal as taught in the specification would be readily incorporated during either an enzymatic synthesis or a chemical synthesis due to the bulky structure of such electron transfer groups which would interfere with the necessary contact between nucleotides. For example, Bannwarth et al. (5,278,043) discloses nucleic acids in which electron transfer compounds are attached to the terminal nucleotides or are substituted for some of the internal nucleotides.

Nucleosides with bulky electron transfer moieties attached are not incorporated during nucleic acid synthesis. The specification simply does not describe a nucleotide with an electron transfer group attached thereto as a discrete molecule as claimed. Nor does the specification teach the claim 27 method of "making a nucleic acid comprising a covalently attached electron transfer moiety" by incorporating a nucleotide triphosphate with covalently attached electron transfer moiety into a nucleic acid "in a synthetic reaction" in view of the previously described method of attaching the ETM after synthesis of the nucleic acid. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. It is clear from the lack of description in the specification that applicant did not contemplate the claimed nucleotide comprising a covalently attached electron transfer moiety and the method of incorporating it during nucleic acid synthesis at the time the claimed invention application was filed.

Response to applicant's traversal

5. Applicant's arguments filed August 21, 2002 have been fully considered but they are not persuasive. It is argued that cited passages in the specification at pages 13, 20-21, 23 and the Examples "provide adequate support for making and using ETM-labeled nucleotides". However, on the contrary, these cited portions describe the method of making nucleic acids comprising electron transfer moieties wherein the nucleotides are modified by addition of an amino group at the 2' or 3' position and the liganded electron transfer moiety is attached via the amino group after synthesis of the nucleic acid in which the amino-modified nucleosides are incorporated (page 20, lines 15-24). As to the prior art present as Exhibits A and B, the handbook Chapter 8, Section 8.2, of the former describes fluorophore-labeled nucleotides compatible with enzymatic oligonucleotide synthesis. This is irrelevant to the claims as fluorophores are not electron transfer moieties. Exhibit B, a J. Am. Chem. Soc. paper by Hurley and Tor, states that it is the first report of a "direct method for the site-specific incorporation of metal complexes during solid-phase oligonucleotide synthesis" (page 2194, first paragraph) wherein the metal complexes are covalently attached via linker at the base of the nucleotide (page 2194, Scheme I). Nevertheless, the specification does not describe a nucleotide with a metal complex attached covalently either via linker or directly as claimed and does not cite any teaching in the prior art that does.

Rejection under 35 U.S.C. 112, second paragraph: Indefiniteness

6. Claims 21-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are confusing with regard to "modified" nucleotide because it is unclear whether the "modification" is the ETM or is some other, additional "modification". Applicant's argument that the specification describes addition of ETMs via attachment to amino modifications on nucleotides in an oligonucleotide does not clarify the claims because the claims do not indicate how the "modification" relates to the ETM.

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Rejection under 35 U.S.C. 102(b): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

N.B.: In view of the lack of written description support for the claimed invention the claims are not entitled to any prior filing date.

7. Claims 21, 4, 25, 27, 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Hurley et al. 1998 (J. Am. Chem. Soc. 120:2194-2195). The claimed invention modified nucleotide triphosphate comprising a covalently attached ETM (claim 21) and embodiments wherein the ETM is a transition metal complex (claim 24) and the metal complex comprises ruthenium (claim 25) are disclosed at page 2194, Scheme I, 6a wherein the modification is the linker. The claimed invention method of making a nucleic acid comprising a covalently attached ETM via steps of providing a modified nucleotide comprising a covalently attached ETM which may be ruthenium, converting the nucleotide into a modified nucleotide triphosphate and incorporating the modified nucleotide triphosphate in a synthetic reaction forming the nucleic acid with attached ETM (claims 27, 30, 31) is disclosed at page 2194, column 2 wherein the "modified" nucleotide is the nucleotide with attached linker.

Rejection under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 22, 23, 26, 28, 29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hurley et al. as applied to claims above, and further in view of Chee et

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al. (6,355,431). The claimed invention modified nucleotide triphosphate comprising a covalently attached ETM and method using same to make a nucleic acid embodiments of claims 22, 23, 28 and 29 differ from the disclosure of Hurley et al. wherein the ETM is attached to ribose and wherein attachment is at the 2' position of the nucleotide. However, attachment of chemical moieties, e.g., label moieties, to ribose at the 2' position of nucleotides was routinely practiced in the art. For example, Chee et al. teach that nucleic acids may be labeled by attachment to the base or to the ribose (column 30, lines 42-54). It would have been obvious and the skilled practitioner in the art would have been motivated to alternatively attach the transition metal complex in Hurley et al. to the ribose based on available materials and techniques and on desired results in view of the teaching of Chee et al. of the essentially equal function of labels in either position. Regarding claims 26 and 32, absent unexpected results it would have been obvious and the skilled practitioner in the art would have been motivated to alternatively employ iron as the transition metal in view of the periodic table of elements.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196. For questions and requests relating to formal matters contact LIE Chantae Dessau at 703-605-1237.

S. Zitomer
Stephanie Zitomer, Ph.D.
May 19, 2003

**STEPHANIE ZITOMER
PRIMARY EXAMINER**